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Graphical Abstract

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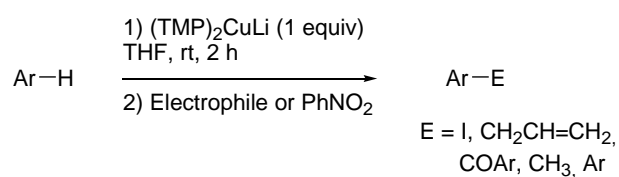
Chimie et Photonique Moléculaires

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Deprotonative cupration of aromatics including heterocycles using the Gilman-type amido-cuprate (TMP)₂CuLi is described.



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LETTERS

New Gilman-type lithium cuprate from a copper(II) salt: synthesis and deprotonative cupration of aromatics

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Abstract— Deprotonative cupration of aromatics including heterocycles (anisole, 1,4-dimethoxybenzene, thiophene, furan, 2-fluoropyridine, 2-chloropyridine, 2-bromopyridine and 2,4-dimethoxypyrimidine) was realized in tetrahydrofuran at room temperature using the Gilman-type amido-cuprate $(\text{TMP})_2\text{CuLi}$ *in situ* prepared from $\text{CuCl}_2\cdot\text{TMEDA}$ through successive addition of 1 equivalent of butyllithium and 2 equivalents of LiTMP. The intermediate lithium (hetero)arylcuprates were evidenced by trapping with iodine, allyl bromide, methyl iodide and benzoyl chlorides, the latter giving the best results. Symmetrical dimers were also prepared from lithium azine and diazine cuprates using nitrobenzene as oxidative agent.

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Keywords: lithium; copper; metalation; aromatic compound; heterocycle

Lithium bases have been largely employed for the deprotonation of aromatic rings.¹ Even if less nucleophilic hindered lithium dialkylamides are more suitable for the metalation of aromatics bearing reactive functions or sensitive π -deficient heterocycles, low reaction temperatures are required due to the high reactivity of the corresponding (hetero)aryllithiums.

The use of bimetallic bases in order to get more efficient and/or more chemoselective reactions is a challenging field. LIC-KOR (LIC = butyllithium, KOR = potassium *tert*-butoxide) first described by Schlosser² and Lochmann,³ and BuLi–LiDMAE (DMAE = 2-dimethylaminoethoxide) introduced by Caubère⁴ and developed further by Gros and Fort in the pyridine series⁵ are well-known examples of synergic (or superbasic) mixtures of organolithiums and alkali metal alkoxides. By combining soft organometallic compounds with alkali (or alkaline-earth metal) additives, bases have been more recently prepared and used to generate functionalized aromatic compounds including heterocycles.⁶ Examples are $\text{R}_2\text{Zn}(\text{TMP})\text{Li}(\cdot\text{TMEDA})$ ($\text{R} = \text{tBu}$, Bu; TMP = 2,2,6,6-tetramethylpiperidino, TMEDA = *N,N,N',N'*-tetramethylethylenediamine) (described by the groups of Kondo, Uchiyama, Mulvey and Hevia),⁷ $(\text{TMP})_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ ⁸ and $\text{TMPZnCl}\cdot\text{LiCl}$ ⁹ (Knochel), $\text{tBu}_3\text{Al}(\text{TMP})\text{Li}$ (Uchiyama and Mulvey),¹⁰ $\text{Al}(\text{TMP})_3\cdot 3\text{LiCl}$ (Knochel),¹¹ $(\text{Me}_3\text{SiCH}_2)_2\text{Mn}(\text{TMP})\cdot\text{Li}\cdot\text{TMEDA}$ (Mulvey),¹² and $\text{MeCu}(\text{TMP})(\text{CN})\text{Li}_2$ (Uchiyama and Wheatley).¹³

We recently accomplished the deprotonation of a large range of aromatics including heterocycles using a newly

developed lithium-cadmium base, $(\text{TMP})_3\text{CdLi}$, *in situ* prepared from $\text{CdCl}_2\cdot\text{TMEDA}$ and 3 equivalents of LiTMP.¹⁴ We here describe the synthesis of putative $(\text{TMP})_2\text{CuLi}$ using the same approach, and its use to deprotonate aromatic substrates.

Wheatley and Uchiyama documented in 2007 the first direct metalation using a lithium cuprate.¹³ The authors showed that Gilman-type amidocuprates prepared from CuI were less efficient bases than Lipshutz-type amidocuprates prepared from CuCN. $\text{MeCu}(\text{TMP})(\text{CN})\text{Li}_2$ was identified as the best base when used at the rate of 2 equivalents in tetrahydrofuran (THF) at 0°C.

Our approach was based on the *in situ* generation of putative $(\text{TMP})_2\text{CuLi}$ from $\text{CuCl}_2\cdot\text{TMEDA}$ ¹⁵ by (i) reduction of Cu(II) to Cu(I) and (ii) formation of the lithium cuprate by addition of two equivalents of LiTMP. The reaction of copper(II) chloride with lithium bis(trimethylsilyl)amide at the reflux temperature of THF being known to produce the corresponding copper(I) amide,¹⁶ the generation of $(\text{TMP})_2\text{CuLi}$ starting from $\text{CuCl}_2\cdot\text{TMEDA}$ and using 3 equivalents of LiTMP was first considered. Electron paramagnetic resonance (EPR) response of Cu(II) was used in order to check the validity of the reduction step using LiTMP. To this purpose, the EPR spectrum of a THF solution prepared from $\text{CuCl}_2\cdot\text{TMEDA}$ and LiTMP (2.10^{-3} M each) was collected, and compared with a spectrum recorded from a THF solution of $\text{CuCl}_2\cdot\text{TMEDA}$ (2.10^{-3} M). It was observed that the reduction to Cu(I) was not quantitative, even after 20 hours at room temperature, and that TEMPO was formed, probably by reaction between LiTMP and dissolved oxygen¹⁷ (Figure 1).¹⁸ It was then

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decided to attempt the use of butyllithium for the reduction of $\text{CuCl}_2 \cdot \text{TMEDA}$ at 0°C , and the EPR spectrum of a THF solution prepared from $\text{CuCl}_2 \cdot \text{TMEDA}$ and BuLi (2.10^{-3} M each) was recorded. The spectrum showing a complete reduction of Cu(II), we prepared the mixed lithium-copper base as depicted in Scheme 1, and recorded again the spectra of the solution. The only observable signal being attributed to TEMPO,¹⁹ the reactivity of such prepared $(\text{TMP})_2\text{CuLi}$ was studied towards various aromatics.

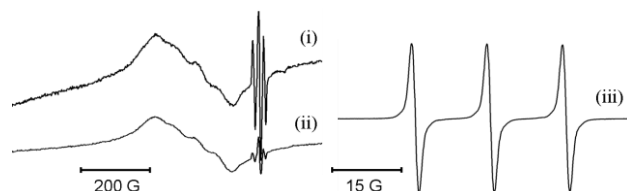
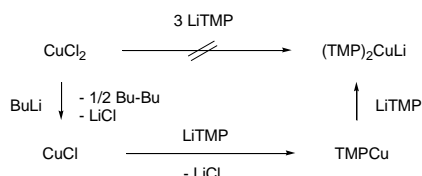


Figure 1. EPR spectra of (i) a THF solution prepared from $\text{CuCl}_2 \cdot \text{TMEDA}$ and LiTMP (2.10^{-3} M each), (ii) the same solution 20 h later and (iii) a THF solution of TEMPO ($g = 2.007$, $a_N = 15.54$ G).



Scheme 1. Synthesis of $(\text{TMP})_2\text{CuLi}$ from $\text{CuCl}_2 \cdot \text{TMEDA}$ as copper(II) source.

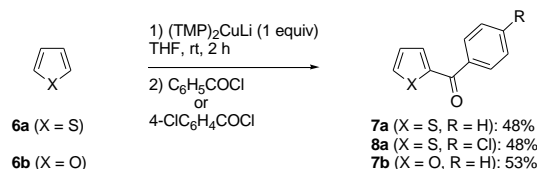
Table 1. Deproto-cupration of **1a,b** followed by trapping with electrophiles.

		1) $(\text{TMP})_2\text{CuLi}$ (1 equiv) THF, rt, 2 h 2) Electrophile	
Entry	Substrate	Electrophile	Product, Yield %
1	1a	I_2	2a , 20
2	1b	I_2	2b , 19
3	1b	$\text{CH}_2=\text{CHCH}_2\text{Br}$	3b , 41
4	1b	$\text{C}_6\text{H}_5\text{COCl}$	4b , 53
5	1b	$4\text{-ClC}_6\text{H}_4\text{COCl}$	5b , 57

With anisole (**1a**) and the 4-methoxy derivative **1b** as substrate, the metalation reactions performed in THF at room

temperature by using 1 equivalent of *in situ* prepared $(\text{TMP})_2\text{CuLi}$, followed by subsequent trapping with elemental iodine after 2 h, proceeded in low yields (compounds **2a**²⁰ and **2b**,²¹ Table 1, entries 1,2). Concomitant formation of 2,2'-dimethoxybiphenyl²² and *N*-(2-methoxyphenyl)-2,2,6,6-tetramethylpiperidine²³ was observed from anisole (**1a**), probably through reactions occurring during the trapping step with iodine. Indeed, it was noted that carrying out the reaction using water as electrophile instead of iodine resulted in recovered anisole. Whereas the use of ethyl acrylate and enones such as 2-cyclohexen-1-one and 2-cyclopenten-1-one did not allow any trapping products, reactions proved successful when performed with allyl bromide and benzoyl chlorides at the reflux temperature of THF (entries 3-5) to afford the allylated derivative **3b**,²⁴ and the benzophenones **4b**²⁵ and **5b**²⁶ in yields ranging from 41 to 57%.

We next demonstrated that the cuprate base was suitable for the metalation of both π -excessive and π -deficient aromatic heterocycles. Thiophene (**6a**) and furan (**6b**) proved to react under the same reaction conditions to furnish after trapping with benzoyl chlorides the expected ketones **7a**,²⁰ **8a**²⁷ and **7b**²⁷ (Scheme 2).






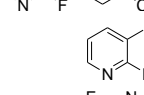


Scheme 2. Deproto-cupration of **6a,b** followed by trapping with benzoyl chlorides.

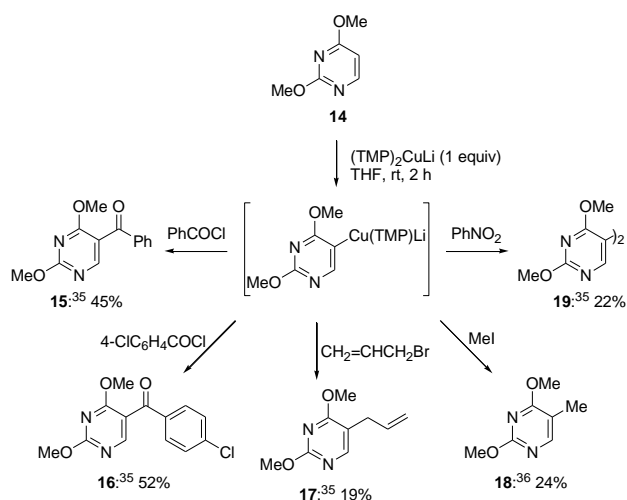
2-Halopyridines **9a-c** were similarly successively treated with the amido-cuprate and benzoyl chlorides. Whereas a low 20% yield (compound **10c**)²⁸ was obtained starting from 2-bromopyridine (**9c**) and using benzoyl chloride, side reactions were not observed with its lighter isomers **9a,b**, and the expected ketones **10a**,²⁹ **10b**³⁰ and **11a**³¹ were isolated in good yields. Using iodine as electrophile in the case of 2-fluoropyridine (**9a**) resulted in the formation of the iodide **12a**²⁰ in a moderate 31% yield due to the concomitant formation of the 3,3'-dimer **13a**.³² The latter was obtained in a high 84% yield using nitrobenzene,³³ which proved to be in this reaction a better oxidant than iodine (Table 2).

2,4-Dimethoxypyrimidine (**14**) was finally similarly involved in the reaction to afford after subsequent trapping with benzoyl chlorides, allyl bromide and iodomethane the regioselectively functionalized derivatives **15-18** in yields ranging from 19 to 52%;³⁴ the corresponding 5,5'-dimer **19** also formed using nitrobenzene as oxidative agent (Scheme 3).

Table 2. Deproto-cupration of **9a-c** followed by trapping with electrophiles or oxidation.

		1) $(\text{TMP})_2\text{CuLi}$ (1 equiv) THF, rt, 2 h 2) Electrophile or $\text{C}_6\text{H}_5\text{NO}_2$	
Entry	Substrate	Electrophile or oxidative agent	Product, Yield %

1	9a	C ₆ H ₅ COCl		10a , 85
2	9b	C ₆ H ₅ COCl		10b , 78
3	9c	C ₆ H ₅ COCl		10c , 20
4	9a	4-ClC ₆ H ₄ COCl		11a , 83
5	9a	I ₂		12a , 31
6	9a	C ₆ H ₅ NO ₂		13a , 84



Scheme 3. Deprotonative cupration of **14** followed by trapping with electrophiles or oxidation.

In summary, deprotonative cupration of aromatics was realized using a Gilman-type amido-cuprate *in situ* prepared from stable CuCl₂·TMEDA.³⁷ The intermediate lithium arylcuprates were notably evidenced by trapping with benzoyl chlorides in satisfying yields.

Further development will notably concern the impact of TEMPO on reaction yields. Indeed, it is known from the literature that TEMPO is an excellent ligand for alkali metals, and its presence in TMP-containing complexes can modify the availability of the amido groups.³⁸

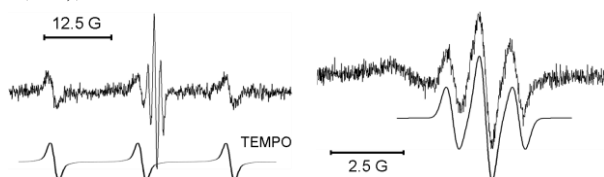
Acknowledgment

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18. An organic radical was also observed ($g = 2.005$, $a_H = 1.096$ G, 2H), but was not identified:



19. TEMPO is similarly formed by preparing LiTMP in THF.
20. The spectral data are analogous to those obtained from a commercial sample.
21. The ^1H NMR data are analogous to those described: Azadi-Ardakani, M.; Wallace, T. W. *Tetrahedron* **1988**, 44, 5939–5952.
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23. ^1H NMR (300 MHz, CDCl_3): δ 0.78 (s, 6H), 1.23 (s, 6H), 1.49–1.64 (m, 6H), 3.75 (s, 3H), 6.82–6.88 (m, 2H), 7.13–7.19 (m, 1H), 7.29 (dd, 1H, $J = 8.3$ and 1.9 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 18.6, 26.0, 31.5, 41.8, 54.4, 55.1, 111.0, 119.3, 126.4, 134.2, 136.0, 160.3.
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30. The ^1H NMR data are analogous to those described: Trécourt, F.; Marsais, F.; Güngör, T.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409–2415.
31. Compound **11a**: yellow powder; mp 90°C ; ^1H NMR (300 MHz, CDCl_3): δ 7.37 (ddd, 1H, $J = 7.6$, 4.9 and 1.9 Hz), 7.44–7.50 (m, 2H), 7.73–7.79 (m, 2H), 8.04 (ddd, 1H, $J = 9.4$, 7.5 and 2.0 Hz), 8.43 (ddd, 1H, $J = 4.9$, 2.1 and 1.2 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 121.3 (d, $J = 30$ Hz), 121.9 (d, $J = 4.5$ Hz), 129.2 (s, 2C), 131.1 (d, 2C, $J = 1.2$ Hz), 135.0 (d, $J = 0.9$ Hz), 140.7 (s), 142.0 (d, $J = 3.3$ Hz), 150.9 (d, $J = 15$ Hz), 160.1 (d, $J = 243$ Hz), 190.7 (d, $J = 4.9$ Hz).
32. Compound **13a**: beige powder; mp 153°C ; ^1H NMR (300 MHz, CDCl_3): δ 7.31–7.36 (m, 2H), 7.88–7.96 (m, 2H), 8.30 (dd, 2H, $J = 4.9$ and 1.9 Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 116.7 (m), 121.7 (m), 142.0 (t, $J = 3.3$ Hz), 148.1 (m), 160.4 (d, $J = 241$ Hz).
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34. Even if the basicity of pyrimidine nitrogens is low compared with that of pyridine, competitive quaternarization by reaction with allyl bromide and methyl iodide is not impossible under the conditions used.
35. Compound **15**: yellow oil; ^1H NMR (300 MHz, CDCl_3): δ 3.95 (s, 3H), 4.07 (s, 3H), 7.42–7.49 (m, 2H), 7.58 (tt, 1H, $J = 7.3$ and 1.3 Hz), 7.74–7.78 (m, 2H), 8.46 (br s, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 54.5, 55.5, 114.5, 128.5 (2C), 129.7 (2C), 133.3, 137.6, 161.2, 166.3, 169.3, 192.2.
Compound **16**: yellow powder; mp 145 – 146°C ; ^1H NMR (300 MHz, CDCl_3): δ 8.48 (s, 1H), 7.68–7.73 (m, 2H), 7.41–7.46 (m, 2H), 4.08 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 54.5, 55.5, 114.1, 128.8 (2C), 130.9 (2C), 136.0, 139.7, 161.3, 166.5, 169.1, 190.9.
Compound **17**: yellow oil; ^1H NMR (300 MHz, CDCl_3): δ 3.22 (m, 2H), 3.96 (s, 3H), 3.97 (s, 3H), 5.00–5.08 (m, 2H), 5.82–5.97 (m, 1H), 7.98 (br s, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 29.8, 54.0, 54.8, 113.6, 116.5, 135.2, 157.0, 164.4, 169.4.
Compound **19**: red powder; mp 209°C ; ^1H NMR (300 MHz, CDCl_3): δ 3.97 (s, 6H), 4.03 (s, 6H), 8.20 (s, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 54.3 (2C), 55.0 (2C), 108.3 (2C), 158.8 (2C), 165.1 (2C), 168.7 (2C).
36. The spectral data are analogous to those previously described: Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, 10, 1715–1718.
37. Typical procedure: To a stirred, cooled (0°C) suspension of CuCl_2 -TMEDA (0.25 g, 1.0 mmol) in THF (5 mL) were successively added BuLi (about 1.6 M hexanes solution, 1.0 mmol) and, 15 min later, a solution of LiTMP prepared in THF (2 mL) at 0°C from 2,2,6,6-tetramethylpiperidine (0.34 mL, 2.0 mmol) and BuLi (about 1.6 M hexanes solution, 2.0 mmol). The mixture was stirred for 15 min at this temperature before introduction of 2,4-dimethoxypyrimidine (125 μL , 1.0 mmol). After 2 h at room temperature, benzoyl chloride (0.24 mL, 2.0 mmol) was added at 0°C . The mixture was stirred for 16 h at 60°C before addition of brine (5 mL) and extraction with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure before purification by column chromatography on silica gel (eluent: heptane/ EtOAc 8:2). Compound **15** (0.11 g, 45%) was isolated as a yellow oil.
38. Forbes, G. C.; Kennedy, A. R.; Mulvey, R. E.; Rodger, P. J. A. *Chem. Commun.* **2001**, 1400–1401. See also: Balloch, L.; Drummond, A. M.; García-Álvarez, P.; Graham, D. V.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Rodger, P. J. A.; Rushworth, I. D. *Inorg. Chem.* **2009**, 48, 6934–6944.